REMARKS

The Official Action dated October 22, 2007 has been carefully considered. Accordingly, the present Amendment is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present amendment, claims 1-20 are cancelled and claims 21-35 are presented. Claim 21 contains limitations from original claims 1 and 2, and the specification, for example at page 5, lines 10-28, while support for claim 22 may be found in the specification at page 3, lines 30-31. Support for claims 23-35 may be found in previous claims 3-6 and 8-16, respectively. These changes are therefore believed to avoid any introduction of new matter, whereby entry of the amendments is believed to be in order and is respectfully requested.

In the Official Action, claim 1 was rejected under 35 U.S.C. §101 on the basis that it was directed to non-statutory subject matter. The Examiner asserted that claim 1 read entirely on mental processes. This rejection is traversed with respect to claims 21-35, and reconsideration is respectfully requested. Specifically, claim 21 recites, inter alia, determining normalized amounts of two or more HPV groups and/or types in a sample "using quantitative nucleic acid amplification." Claim 21 therefore recites non-mental steps and consequently contains statutory subject matter under 35 U.S.C. §101. Accordingly, the rejection under 35 U.S.C. §101 has been overcome and reconsideration is respectfully requested.

Claims 1-20 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. First, the Examiner asserted that claim 1 was incomplete as it omitted essential steps, namely an amplification step, how the amplification is determined, and calculation parameters for

establishing a standard curve wherein estimating the risk can be determined. The Examiner objected to claims 10-12 on the basis that there was insufficient antecedent basis for the risk estimation values in step (iii) and asserted that odds ratio, relevant risk and positive predictive values have not been defined. Further, the Examiner objected to the phrase "wherein the human being is a woman and the carcinoma is cervical carcinoma in situ" in claims 13-16 as having insufficient antecedent basis.

This rejection is traversed with respect to claims 21-35, and reconsideration is respectfully requested. Specifically, claim 21 recites a step of determining normalized amounts of two or more HPV groups and/or types in a sample from said human being using quantitative nucleic acid amplification of said HPV groups and/or types, wherein said determining comprises normalizing results of the quantitative nucleic acid amplification for the amount of cells sampled, and a step of estimating a combined risk for carcinoma development for said human being from individual risk estimation curves of the respective two or more HPV groups and/or types. Thus, claim 21 sets forth how the normalized amounts are determined, i.e., using quantitative nucleic acid amplification and normalizing results of the quantitative nucleic acid amplification for the amount of cells sampled. While PCR is a common amplification technique which may be employed in the present methods, other amplification techniques are known in the art and may be employed in the present methods. See, for example, page 3, lines 30-31 and page 5, line 9-page 6, line 3 of the present specification.

Further, claim 21 defines the estimating step as employing individual risk estimation curves. These curves are standard curves prepared as described in the specification, for example at pages 7-9, examples of which are included in the figures of the present application and

discussed in detail at pages 15-16. Thus, the present specification provides antecedent basis for the steps recited in claim 21 and claim 21 is definite to one of ordinary skill in the art in view of the present specification.

Claims 25 and 29-31 recite that the individual risk estimation curves provide odds ratio (OR), relative risk (RR) and/or positive predictive values (PPV). While the Examiner has asserted that these parameters are undefined in the specification, Applicants submit that these terms are well known to one of ordinary skill in the relevant art. For example, the Examiner's attention is directed to the National Library of Medicine's Online Dictionary (http://www.nlm.nih.gov/nichsr/hta101/ta101014.html) wherein the following definitions are provided:

Odds ratio: a measure of treatment effect that compares the probability of a type of outcome in the treatment group with the outcome of a control group, i.e., [Pt ÷ (1 - Pt)] [Pc ÷ (1 - Pc)]. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the odds ratio of survival would be [0.10 ÷ (1.0 - 0.10)] ÷ [(0.25 ÷ (1.0 - 0.25)] = 0.33. (See also absolute risk reduction, number needed to treat, and relative risk.).

Relative risk reduction: a type of measure of treatment effect that compares the probability of a type of outcome in the treatment group with that of a control group, i.e.: (Pc - Pt) ÷ Pc. For instance, if the results of a trial show that the probability of death in a control group was 25% and the probability of death in a control group was 10%, the relative risk reduction would be: (0.25 - 0.10) ÷ 0.25 = 0.6. (See also absolute risk reduction, number needed to treat, and odds ratio.).

Predictive value positive: an operating characteristic of a diagnostic test; predictive value positive is the proportion of persons with a positive test who truly have the disease, determined as: [true positives ÷ (true positives + false positives)]. It varies with the prevalence of the disease in the population of interest. (Contrast with predictive value negative.).

As these terms are well defined in the art, claims 25 and 29-31 are definite to one of ordinary skill in the art.

Finally, claims 26 and 32-35 recite that the human being is a woman and the carcinoma is cervical carcinoma in situ. The examples set forth in the present specification are specifically directed to a method for estimating the risk for development of cervical carcinoma in situ in women. Accordingly, the present specification provides antecedent basis for these claims.

It is therefore submitted that claims 21-35 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-20 were also been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserted that the field of viral detection and risk assessment of viral particle detection to a cause of cancer is rather unpredictable and the claimed invention does not set forth the parameters that are required to determine the risk posed by a particular HPV sample or types. The Examiner specifically referred to pages 15 and 16 of the present specification regarding the importance of OR curves and their ability to be able to accurately estimate risks and that merely counting the total number of HPV copies underestimates the risk, and the claims do not reflect such teachings.

This rejection is traversed with respect to claims 21-35, and reconsideration is respectfully requested. Specifically, claim 21 recites a step of determining normalized amounts of two or more HPV groups and/or types in a sample from said human being using quantitative nucleic acid amplification of said HPV groups and/or types, wherein said determining comprises normalizing results of the quantitative nucleic acid amplification for the amount of cells sampled, and a step of estimating a combined risk for carcinoma development for said human being from individual risk estimation curves of the respective two or more HPV groups and/or types. Thus, according to claim 21, the present methods do not merely use the amount of total HPV copies, but rather count amounts of individual HPV groups and/or types (i.e., at least two groups, at least two types, or at least one group and one type), and further requires normalizing results of the quantitative nucleic acid amplification for the amount of cells sampled. The normalization and use of the individual risk estimation curves of the respective HPV groups and/or types safeguards against underestimates discussed at page 16 of the present specification resulting from merely counting the total number of HPV copies. Although the Examiner fails to specifically indicate how the detailed example and data set forth in the specification fail to enable the claimed method, a review of the detailed disclosure of the present specification shows that the steps of claim 21 in fact provide an improved method for estimating the risk for development of carcinoma in a human being exposed to HPV.

It is therefore submitted that claims 21-35 are fully enabled by the present specification in accordance with the requirements of 35 U.S.C. §112, first paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Finally, claims 1 and 2 were rejected under 35 U.S.C. §102(b) as being anticipated by the Josefsson et al, *Journal of Clinical Microbiology*, 37(3):490-496 (1999), cited in Applicants' Information Disclosure Statement and in the present specification. The Examiner asserted that Josefsson et al teach a method of detection and quantification of a single or one HPV using PCR and asserted that this would lead to an estimation of risk.

This rejection is traversed with respect to claims 21-35, and reconsideration is respectfully requested. Specifically, claim 21 recites a step of determining normalized amounts of two or more HPV groups and/or types in a sample from said human being using quantitative nucleic acid amplification of said HPV groups, wherein said determining comprises normalizing results of the quantitative nucleic acid amplification for the amount of cells sampled, and a step of estimating a combined risk for carcinoma development for said human being from individual risk estimation curves of the respective two or more HPV groups and/or types.

On the other hand, Josefsson discloses a method for the detection and quantification of HPV using fluorescent 5' exonuclease assay. However, Applicants find no teaching by Josefsson et al of a method employing quantitative nucleic acid amplification and normalization of the results of the quantitative nucleic acid amplification for the amount of cells sampled for two or more HPV groups and/or types, in combination with the use of individual risk estimation curves of the respective two or more HPV groups and/or types for a combined risk estimation.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). In view of the failure of Josefsson to

teach the combination of normalization of the results of the quantitative nucleic acid amplification for the amount of cells sampled for two or more HPV groups and/or types, and the use of individual risk estimation curves of the respective two or more HPV groups and/or types to provide a combined risk estimation, Josefsson et al do not describe, either expressly or inherently, each and every element as set forth in claim 21. Thus, Josefsson et al do not anticipate claim 21 or any of claims 22-35 dependent thereon. Accordingly, the rejection under 35 U.S.C. §102 has been overcome, and reconsideration is respectfully requested.

It is believed that the above demonstrates the patentability of present claims, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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CINCINNATI/147289 v.01